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# Q fever and spontaneous abortion

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## Abstract

Q fever, caused by *Coxiella burnetii*, may result in abortions in infected animals and pregnant women. However, the role that Q fever plays in spontaneous abortions is still unknown. This study examined the association between Q fever serology and abortion in a region where Q fever is endemic. A case–control population-based study was conducted in General Yagüe Hospital (Burgos area, Spain) between June 2009 and July 2010. A total of 801 samples from 500 pregnant women were tested, of whom 273 had a spontaneous abortion and 227 gave birth. IgG and IgM antibody titres against Q fever were determined in their two phases (I and II) by immunofluorescence assay. Seropositivity (phase I IgG $\geq$1:16 or phase II IgG $\geq$1:80) was detected in 88/273 (32.2%) cases and 53/227 (23.3%) controls; $p < 0.01$, OR 1.5, 95% CI 1.0–2.3. Seropositivity for both phases of IgG, compatible with recent or persistent infection, was detected in 55 (20.1%) vs 22 (9.7%); $p < 0.001$, OR 2.3, 95% CI 1.3–3.9. High phase II IgG antibodies compatible with active or recent infection (titres $\geq$1:160) were detected in 27 (9.6%) vs 7 (3.1%); $p < 0.002$, OR 3.4, 95% CI 1.4–8.0, respectively. Q fever was diagnosed in 14 (5.1%) cases. The risk of abortion associated with serological markers of active or recent Q fever in pregnant women was measurable and noticeable in this population, and accounted for 12% (95% CI 4–21%).

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## Introduction

Q fever is a worldwide zoonosis caused by *Coxiella burnetii* [1]. Cattle and farm animals are the main reservoirs of the microorganism [1–3]. Infected animals suffer from spontaneous abortions and other obstetric complications [3]. Humans are mainly infected through inhalation of contaminated aerosols [1,2]. Q fever is usually an occupational disease, although isolated cases and outbreaks have been reported in people who have had indirect contact with infected animals [1,2]. Acute Q fever has a wide clinical spectrum, although the majority of cases are asymptomatic [1,2]. Endocarditis represents the main complication of the chronic form [1,4]. Serology is the cornerstone of diagnosis and immunofluorescence assay is the current reference method for the serodiagnosis of Q fever [5–7].

Spontaneous abortion affects 10–20% of pregnancies but its cause remains unknown in more than 50% of cases [8]. There is currently no evidence that intrauterine infections are significantly associated with abortion in humans [9]. Fever data are available on the consequences of Q fever during pregnancy. This infection acquired in the first trimester is a serious disease and frequently results in abortion [10–13]. In pregnant women and other mammals the bacteria will colonize and multiply in the uterus and placenta, and be reactivated during subsequent pregnancies [11–15]. For this reason, it is conceivable that active Q fever may be associated with abortion. However, the role that Q fever plays in spontaneous abortions is still unknown.

The aim of the present study was to evaluate the relationship between Q fever serology and spontaneous abortions among women in a region where Q fever is endemic.

## Methods

### Study design

A case–control population-based study was conducted in General Yagüe Hospital (Burgos area, Spain) between June 2009 and July 2010 (13 months). A total of 2435 women were admitted to our hospital for delivery at this time and 433 women having abortions (approximately 15% prevalence); from these, 273 having a spontaneous abortion (cases) and 227 giving birth (controls) were enrolled in the study. Our hospital is the only facility providing maternity care to our health area (population about 220 000). The study protocol was reviewed and approved by the hospital Clinical Research Ethics Committee. All the women included in the study signed an informed consent form.

### Selection and classification of patients

Both the control women and those with abortions were selected at random, at a rate of about five per week in each group. It was decided not to include women in the control group with a previous complicated obstetrics history or complicated partum because we do not know to what degree an infection reactivated by Q fever influences these aspects [10,12]. For this reason, and to make the control group more representative, it was decided to exclude controls with a current or previous complicated partum or pregnancy. An intrauterine product of conception was considered as a pregnancy. Therefore, extrauterine pregnancies were excluded. All miscarriages were confirmed by ultrasound or pathological examination after uterine curettage. According to the WHO a spontaneous abortion is "the expulsion or extraction from its mother of an embryo or foetus weighing 500 g or less" [16]. It typically corresponds to a gestational age of 20–22 weeks or less [8]. The epidemiological and clinical data were obtained using a personalized questionnaire collected before the serology test results were available. Past medical history was examined and patients with relevant serology were contacted to collect additional data and for follow-up. Contact with cattle was defined as habitual contact with farm animals (veterinarian, livestock farmer, butcher, farm worker), consumption of uncontrolled milk products, or contact with products from animal sources or with animal manure [1,2]. Except for age, we did not find any risk factors common to being *C. burnetii* seropositive and spontaneous abortion [8].

### Serological and laboratory methods

Q fever IgM and IgG (phase I and II antigen) were determined by immunofluorescence assay using reagents and test protocols from Focus Technologies (formerly MRL, Cypress, CA, USA). Blood samples were collected by venepuncture, and serum samples were stored at −20°C until analysis [6]. Titres equal to or greater than IgG II (1:80), IgG I (1:16), IgM I (1:16) and IgM II (1:10), were considered positive. The first serological determination was performed after partum or abortion (<48 h). In all cases a second sample was obtained 2 or 3 weeks after abortion. A second sample was obtained from the controls at 2 or 3 weeks after partum when the titres were high (at least twice the threshold for seropositivity). Furthermore, in both cases and controls, at least one more serology sample was obtained every 2–3 weeks from the last serology performed if there were increased titres. Our laboratory was not aware of the source of the samples nor did it have any clinical information about them. Q fever is defined solely by serological criteria based on the frequent asymptomatic nature of infection during pregnancy [10–13]. Post-abortion seroconversion, or a fourfold increase or decrease in specific antibodies titres, was diagnostic of Q fever [6,7]. We cannot exclude acute or recent infection with high phase II IgG antibodies (titres ≥1:160) [7,17]. A diagnosis of chronic Q fever was made with an IgG phase I titre of ≥1:800 in at least two consecutive samples and a specific chronic infectious syndrome [7]. In cases and controls the following analyses were performed on one or more occasions: white cell count, platelet count, general biochemistry parameters, liver enzymes, plasma coagulation, urine sediment and analysis, C-reactive protein, erythrocyte sedimentation count, white blood cell count and serology for *Toxoplasma gondii*, *Treponema pallidum*, rubella virus, cytomegalovirus, hepatitis B virus and human immunodeficiency virus. Other serology was carried out in abortions in case of fever or general clinical symptoms: herpes simplex viruses 1 and 2, parvovirus B19, *Brucella melitensis*, *Mycoplasma pneumoniae*, Epstein–Barr virus, *Chlamydia pneumoniae*, influenza viruses A and B, adenovirus, respiratory syncytial virus and *Legionella pneumophila*. Other diagnostic tests were performed at the discretion of an experienced internist.

### Statistical analysis

To determine the sample size, data obtained from a population sample from southern France was used as a reference (15% for phase II IgG >1:100) [17]. The *Z*-statistic was applied for comparison of dichotomous variables, expecting to observe an OR ≥2. Any OR with a confidence interval that excluded unity would be considered as clinically relevant. If we assumed an $\alpha$ risk of 5% and a $\beta$ risk of 10% and given the one-sided character of the alternative hypothesis, the minimum sample size was calculated to be 197 cases. The collection of data was extended for a minimum period of 1 year to correct for possible seasonal bias of the primary acute Q fever incidence peak [1,2]. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Data were analysed using Fisher's exact test or Mann–Whitney *U*-test, depending on the type of variable. The 'attributable risk per cent' in case–control studies was computed by means of the Cole and MacMahon method [18]. A p value <0.05 was considered to be statistically significant. We decided to use a one-sided p value as all the evidence points to the directionality of this relationship only going one way.

## Results

A total of 801 samples were tested; one sample was analysed for 245 women and two or more for 255 women. Seventeen women with abortions and 28 control women were previously excluded because they did not sign the informed consent. Patient characteristics and serological results are summarized in Table 1. There was an association between IgG titres compatible with active or recent Q fever and spontaneous abortion. Age, time of residence in Burgos, contact with cattle and cohabitation with pets were also associated with abortion. In a multivariate logistic regression adjusted for these variables, spontaneous abortion (OR 3.4, 95% CI 1.4–8.1) and age (OR 1.7, 95% CI 1.2–2.5) remained associated with increased titres for *Coxiella*. If the proportion of the population exposed (active or recent Q fever) was 11.4% ($P_e$) and the estimated relative risk was 2.3 (95% CI 1.41–3.52) ($R$), then the attributable risk per cent ($A_e$%) of associated abortion [$A_e\% = P_e(R - 1)/1 + P_e(R - 1) \times 100$] [18] was 12% (95% CI 4–21%).

We also took into account anembryonic pregnancies (early abortions caused by chromosomal abnormalities in about 90% of cases) and other possible causes of abortion (Table 3) [16]. When studying just the 192 cases without these characteristics, this association increases [24/192 (12.5%) vs 7/227 (3.1%); p <0.001, OR 4.5, 95% CI 1.8–10.6]. The same happened with those who had seropositivity for both phases of IgG [41 (21.4%) vs 7 (3.1%); p <0.001, OR 2.5, 95% CI 1.4–4.5], and seropositivity for both phases of IgG or high phase II IgG titres [45 (23.4%) vs 7 (3.1%); p <0.001, OR 2.8, 95% CI 1.6–4.9].

There was a difference in distribution of phase II IgG titres in the two study groups (Table 2). IgM antibodies were observed in only one case of abortion. Q fever was diagnosed in 14 (5.1%) cases: seroconverted (two women), fourfold increase IgG titres (three womrn), fourfold decrease (eight women). Two controls with initial high IgG titres also showed significant serological changes: one an increase and the other a decrease. Only one woman with an abortion and high phase II IgG titres suffered mild general symptoms. Two women (one case and one control) had more than three consecutive phase I IgG titres in the chronic Q fever range. However, these patients remained asymptomatic and trans-thoracic and trans-oesophageal ultrasonography as well as PCR assays of their blood were negative. No seasonal trends were observed in these women. We did not find significant differences in the frequency whether the abortions were early or late (>12 weeks of gestation) as regards seropositivity.

Differences in white cell count (p 0.03) and C-reactive protein values (p 0.005) between seropositive and seronegative cases were detected (Table 3). On classifying by subgroups, these differences were independent from the presence of other infections, fever, or general symptoms. IgM antibodies were positive against *Mycoplasma pneumoniae* in three women with abortions, and were positive in one woman each against herpes simplex virus 1, herpes simplex virus 2 and varicella zoster virus. One woman with abortion

**TABLE 1. Patient characteristics and serological results of 500 pregnant women**

| | Cases (*n* = 273) | Controls (*n* = 227) | p value | OR | 95% CI |
|---|---|---|---|---|---|
| Age (years) | 34 (31–38) | 32 (24–35) | <0.001 | – | – |
| Time in Burgos (years) | 28 (8–35) | 25 (5–33) | 0.01 | – | – |
| Born in Spain | 226 (82.8) | 183 (80.6) | 0.56 | 1.1 | 0.7–1.8 |
| Rural life[a] | 57 (20.9) | 54 (23.6) | 0.25 | 1.1 | 0.7–1.8 |
| Caucasian ethnicity | 240 (88.6) | 194 (87.0) | 0.34 | 1.1 | 0.6–1.9 |
| Contact with cattle | 31 (11.4) | 13 (5.7) | 0.01 | 2.1 | 1.0–4.1 |
| Contact with pets | 84 (30.8) | 51 (22.5) | 0.02 | 1.5 | 1.0–2.2 |
| Serology | | | | | |
| IgG I ≥16 or IgG II ≥80[b] | 88 (32.2) | 53 (23.3) | 0.01 | 1.5 | 1.0–2.3 |
| IgG I ≥16 and IgG II ≥80[c] | 55 (20.1) | 22 (9.7) | 0.001 | 2.3 | 1.3–3.9 |
| IgG II ≥160[d] | 27 (9.9) | 7 (3.1) | 0.002 | 3.4 | 1.4–8.0 |
| (IgG I ≥16 and IgG II ≥80) or IgG II ≥160 | 59 (21.6) | 22 (9.7) | 0.001 | 2.5 | 1.5–4.3 |

Quantitative variables expressed as median and interquartile range. Dichotomous variables expressed as *n* (%); Mann–Whitney *U*-test or Fisher's exact chi-squared test (one-sided), according to the type of variable; Cases, pregnant women with spontaneous abortion; Controls, pregnant women with no history of abortion or obstetric complications in the current pregnancy or previous pregnancies.
[a]Population <10 000 inhabitants.
[b]Seropositivity.
[c]Serological titres compatible with recent, persistent or recrudescent infection.
[d]An active or recent infection cannot be excluded.

**TABLE 2. Distribution of serological IgG titres against *Coxiella burnetii***

| | Cases (*n* = 273) | Controls (*n* = 227) | p value |
|---|---|---|---|
| IgG phase I | | | 0.18 |
| <16[a] | 206 (75.5) | 189 (83.3) | |
| 16 | 42 (15.4) | 28 (12.3) | |
| 32 | 11 (4.0) | 6 (2.6) | |
| 64 | 9 (3.3) | 2 (0.9) | |
| 128 | 2 (0.7) | 0 (0.0) | |
| 256 | 2 (0.7) | 1 (0.4) | |
| 512 | 0 (0.0) | 1 (0.4) | |
| 1024 | 1 (0.4) | 0 (0.0) | |
| IgG phase II | | | 0.009 |
| <80[a] | 203 (74.4) | 189 (83.3) | |
| 80 | 43 (15.8) | 31 (13.7) | |
| 160 | 14 (5.1) | 3 (1.3) | |
| 320 | 7 (2.6) | 1 (0.4) | |
| 640 | 5 (1.8) | 3 (1.3) | |
| 1280 | 0 (0.0) | 0 (0.0) | |
| 2560 | 1 (0.4) | 0 (0.0) | |

Fisher's exact chi-squared test (one-sided). Expressed as *n* (%).
[a]Negative titres.

**TABLE 3. Characteristics of abortions to study according to their *C. burnetii* serostatus**

| | Positive (*n* = 88) | Negative (*n* = 185) | p value |
|---|---|---|---|
| Age | 34 (31–38) | 34 (31–37) | 0.33 |
| Time in Burgos | 30 (9–36) | 25 (8–34) | 0.19 |
| Born in Spain | 77 (87.5) | 149 (80.5) | 0.10 |
| Rural life[a] | 21 (23.9) | 36 (19.5) | 0.24 |
| Caucasian ethnicity | 81 (93.1) | 159 (86.4) | 0.76 |
| Contact with cattle | 14 (15.9) | 17 (9.2) | 0.07 |
| Contact with pets | 27 (30.7) | 57 (30.8) | 0.55 |
| Fever (>37°C) | 10 (11.4) | 15 (8.2) | 0.25 |
| General symptoms[b] | 10 (11.4) | 41 (22.3) | 0.02 |
| Miscarriage late (>12 week) | 6 (6.9) | 16 (8.8) | 0.39 |
| Abortions (≥2) | 23 (26.1) | 59 (31.9) | 0.51 |
| Multiparity (≥2 births) | 8 (9.1) | 26 (14.1) | 0.16 |
| Pregnancies (≥2) | 53 (60.2) | 123 (66.8) | 0.17 |
| Anembryonic pregnancy | 7 (8.0) | 8 (4.3) | 0.17 |
| Concurrent causes of abortion | 18 (20.5) | 51 (27.6) | 0.13 |
| Endocrine pathology | 5 (5.7) | 17 (9.2) | – |
| Anatomic abnormalities | 3 (3.4) | 9 (4.9) | – |
| Neoplastic or autoimmune disease | 3 (3.4) | 14 (7.6) | – |
| Others infections | 4 (4.5) | 4 (2.2) | – |
| Invasive procedures and others | 3 (3.4) | 7 (3.7) | – |
| Elevated liver enzymes | 9 (10.2) | 14 (7.6) | 0.31 |
| White blood cell count ($\times 10^9$/L), median | 8.3 (7.2–9.8) | 7.6 (6.2–9.4) | 0.03 |
| Platelet counts ($\times 10^9$/L) | 245 (60.1) | 249 (55.7) | 0.59 |
| Sedimentation count (mm/h) | 8 (5–11) | 6 (4–10) | 0.05 |
| C-reactive protein (mg/L) | 2 (0.5–4.5) | 0.5 (0.5–3) | 0.005 |

Quantitative variables expressed as median and interquartile range. Dichotomous variables expressed as *n* (%); Mann–Whitney *U*-test or Fisher's exact chi-squared test (one-sided), according to the type of variable.
[a]Population <10 000 inhabitants.
[b]The presence of at least three of the following in the 15 days before the miscarriage: fever (>37°C), chills, muscle and/or joint pains, headaches, flu-like symptoms or weakness.

suffered a symptomatic *Escherichia coli* urinary infection and another had acute sinusitis caused by *Haemophilus influenzae*.

## Discussion

This study demonstrates a strong association between serological titres consistent with acute or recent Q fever and spontaneous abortion. This relationship is in agreement with previous human observations. Spontaneous abortion was observed in 13.5% of 53 [12] and seven of seven [10] pregnant women with first-trimester untreated primary Q fever. Some serosurvey studies in different populations have examined this association and found contradictory results. In 12 716 recently pregnant women in an area of France where Q fever is endemic, seroprevalence of recent or chronic infections was three times higher among women who had a spontaneous abortion. However, the number of infected women was too small and statistical significance was not achieved. In 438 women seen in a Recurrent Miscarriage Clinic in London, no association was found between phase II IgG titres ≥1:50 (4.6%) and miscarriage [19]. However, in 2394 subjects from Ireland, women with a history of miscarriage or prematurity were more often seropositive than those without such a history (19.5% vs 9.8%, p <0.001) [20].

The absence of general symptoms in pregnant women does not rule out an active infection in the presence of relevant titres [10–12]. This was shown during an outbreak in the French Alps, where only one out of 11 pregnant women with Q fever had symptoms, compared with 48 out of 54 non-pregnant women [4]. We report an increased median white blood cell count and C-reactive protein levels in patients with positive serology. Despite being significant, such a difference is extremely limited and has no clinical relevance. The increase in C-reactive protein was the only analytical marker that significantly differentiated between inpatients and outpatients with primary acute Q fever during a large outbreak in the Netherlands [21]. However, all of these patients had a C-reactive protein >10 mg/L.

Post-abortion serological changes were diagnostic of active infection in 14 (5.1%) cases. However, the main pathogenic mechanisms involved in this association appear to be related to a secondary or recrudescent infection [6]. This is suggested by the absence of IgM antibodies [1,7] and the high frequency of early seropositivity for both phases of IgG [6]. This has been illustrated in a study with guinea-pigs, where re-exposure to *C. burnetii* phase I (virulent) 105 days after the primary infection induced an early phase I and II IgG antibody response [22]. Data related to the intensity of the anamnesic immune response are contradictory. In the previously mentioned experimental model, an increase in phase II IgG antibodies was less than expected [22]. The reactivation of Q fever as the result of pregnancy in mice is also accompanied by little or no variation in serological values [15]. However, after cardiac surgery in humans there can be a significant increase in IgG titres compatible with reactive Q fever [23]. The low frequency with which very high IgG II titres were found could indicate a mild immune response after infectious reactivation or inhibition by a decrease in the infection load after miscarriage [6].

Isolation of bacteria is normally required to prove that active infection did indeed occur. However, in this case it could be difficult, because this infection tends to be local (intrauterine) and focal in these circumstances [5,12,13]. This was illustrated in a Canadian study, where an association was observed between seropositivity (291/7658) against *C. burnetii* and previous or current neonatal death. However, no placental samples from 153 seropositive women showed signs of Q fever by PCR [13]. In a French study, 21% (5/23) of pregnant women with Q fever diagnosed by serology had obstetric complications, but bacteria could not be identified in any of them in the placenta or the fetus by PCR or culture [12]. However, in another series, all the women were seropositive when *Coxiella* was identified (19/74) using PCR in some of the many samples analysed, in both the mother and the fetus [5]. In conclusion, bacterial isolation techniques based on obtaining biological samples are of limited diagnostic use, with serology being the best method for confirming the disease in pregnant women.

The validity of the results is demonstrated by the absence of serological cross-reactivity with other zoonoses and common infections [19,24] and repeat samples in almost all women with high titres [6,7]. The possible bias associated with changes in the immune system during pregnancy virtually disappears with the control group used [25].

These results need to be confirmed in other areas where Q fever is endemic. It must be determined whether the obstetric outcome of seropositive pregnant women with relevant titres is changed with specific antibiotic therapy. It has been shown that the administration of cotrimoxazole for 35 days to pregnant women with primary Q fever decreases fetal mortality and placental infection [12]. In conclusion, our results suggest that the association between Q fever and spontaneous abortion is much higher than was thought. We confirm the need for serological monitoring of Q fever in pregnant women from endemic areas [10,11].

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## Transparency Declaration

The authors have no conflicts of interest to declare.

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